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Prospective Study of Risk Factors for Esophageal and Gastric Cancers in the Linxian General Population Trial Cohort in China

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Esophageal cancer incidence and mortality rates in Linxian, China are among the highest in the world. We examined risk factors for esophageal squamous cell carcinoma (ESCC), gastric cardia cancer (GCC), and gastric noncardia cancer (GNCC) in a population-based, prospective study of 29,584 adults who participated in the Linxian General Population Trial. All study participants completed a baseline questionnaire that included questions on demographic characteristics, personal and family history of disease, and lifestyle factors. After 15 years of follow-up, a total of 3,410 incident upper gastrointestinal cancers were identified, including 1,958 ESCC, 1,089 GCC and 363 GNCC. Cox proportional hazard models were used to estimate risks. Increased age and a positive family history of esophageal cancer (including ESCC or GCC) were significantly associated with risk at all 3 cancer sites. Additional risk factors for ESCC included being born in Linxian, increased height, cigarette smoking and pipe smoking; for GCC, male gender, consumption of moldy breads and pipe smoking; and for GNCC, male gender and cigarette smoking. Protective factors for ESCC included formal education, water piped into the home, increased consumption of meat, eggs and fresh fruits and increased BMI; for GCC, formal education, water piped into the home, increased consumption of eggs and fresh fruits and alcohol consumption; and for GNCC, increased weight and BMI. General socioeconomic status (SES) is a common denominator in many of these factors and improving SES is a promising approach for reducing the tremendous burden of upper gastrointestinal cancers in Linxian.

Key words: gastric cardia cancer; gastric noncardia cancer; cohort studies; diet; smoking

Esophageal cancer is the sixth most common cause of cancer-related death worldwide.[1] Some of the world's highest incidence and mortality rates of esophageal cancer occur in China.[2,3] Considerable geographic variation exists in these rates across the country, with the most prominent cluster seen in North Central China, particularly in Lin county (Linxian).[3,4] Esophageal cancer mortality rates in Linxian exceed the Chinese average rates by 10-fold and the rates among Caucasian Americans by 100-fold.[5] In Linxian, esophageal squamous cell carcinoma and gastric cardia cancer are both frequent and have traditionally been considered a single disease, esophageal cancer, because of their similar symptoms. Reasons for the unusually high rates of esophageal and gastric cardia cancers in the Linxian population are unclear, but recent reports suggest that rates have begun to decline.[6]

Although tobacco smoking and alcohol drinking account for over 90% of esophageal squamous cell carcinoma in the West,[7,8] previous studies have shown that they are not important contributing factors to the development of cancer in Linxian.[9,10] The geographic variation in occurrence in China strongly suggests that environmental or lifestyle factors are major contributors to the etiology of esophageal/gastric cardia cancer. Diet has received particular attention as a critical contributing factor for the excess cancer rates in Linxian because many surveys have documented poor overall nutritional status and deficiencies in vitamins A, B_2, C, E, selenium, zinc and calcium in this area.[4,11,12] The extraordinary esophageal/gastric cardia cancer rates coupled with documented poor nutritional status were the impetus for the conduct of 2 large nutrition intervention studies in the late 1980s that showed that the combination of selenium/vitamin E/β-carotene significantly reduced total mortality, total cancer mortality, and stomach cancer (primarily GCC) rates.[13,14] Subsequently, prospective biochemical studies in this same trial cohort showed strong protective associations for ESCC and GCC in participants with high baseline serum selenium concentrations;[15] similar protective associations for serum vitamin E concentrations were also demonstrated.[16] Although the role of nutrition in the etiology and prevention of upper gastrointestinal cancer has been established through these intervention and biochemical epidemiologic studies, it has been much more difficult to link risk with dietary intake of foods assessed *via* questionnaire. Neither low consumption of potentially beneficial foods (*e.g.*, fruits, vegetables, meat and eggs) nor high consumption of potentially harmful foods (*e.g.*, pickled or moldy food and millet) has been convincingly linked to cancer risk in this population.[9,10,17] Among all the risk factors evaluated by questionnaire to date, only a family history of esophageal or gastric cancer has emerged as a consistent risk factor,[9,10,17] although not a strong one.

We reported previously a 5-year prospective analysis of risk factors for esophageal and gastric cancers in the Linxian General Population Trial.[9] To study these risk factors in greater detail and to look at risk factors by anatomic subsites, we continued to follow the participants for an additional 10 years. We present results based on 15 years of follow-up in this population-based, prospective cohort of 29,584 adults and we examine risk factors for esophageal squamous cell carcinoma (ESCC), gastric cardia cancer (GCC) and gastric non-cardia cancer (GNCC) among the 3,410 documented incident cases.

Subjects and methods

Study cohort

A detailed description of the Linxian General Population Trial has been reported previously.[13,14] Briefly, 29,584 individuals, 40–69 years of age at baseline, with no history of cancer or debilitating disease, were recruited from the general population of Linxian. In 1984, all study participants were interviewed to complete a baseline questionnaire that covered questions on demographic characteristics, personal and family history of cancer and other diseases, and lifestyle factors, including age, birthplace, height, weight, education, occupation, diet, drinking habits (hot liquids in summer and winter), tobacco and alcohol use and water supply. Height and weight were measured at baseline as part of the physical examination. The dietary section of the questionnaire included nine food items (persimmon bread, food cooked in oil or had oiled added to it, meat [pork, beef, rabbit, chicken, or duck], eggs, fresh vegetables, pickled vegetables, moldy vegetables, fresh fruits and moldy bread) and participants were asked about the

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frequency of intake in the past 12 months (times/day, times/week, times/month, times/year, or never ate) for each food item. The food questionnaire was not validated. All participants were randomly assigned to 1 of 8 vitamin/mineral combinations, and the supplements were distributed from March 1986 through May 1991. During the 5.25 year intervention period, cancer diagnoses among the study subjects were ascertained through monthly visits by village health workers, contact with local commune and county hospitals, and a study medical team in Linxian that provided clinical and diagnostic services; 85% of the cases were verified by a review panel of senior Chinese and American experts in gastroenterology, radiology, cytology, and pathology. In the subsequent 10 years post-trial, study subjects were contacted monthly by either village health workers or interviewers, and cancer diagnoses were verified by senior Chinese diagnosticians from Beijing. Case ascertainment is considered complete and loss to follow-up minimal ($n = 176$ or $<1\%$). Human subject protection procedures were followed in accord with those prescribed by the U.S. National Institutes of Health and the Cancer Institute, Chinese Academy of Medical Sciences.

Statistical analysis

Person-years of follow-up were calculated from the start of the study period (March 1986) until the date of cancer diagnosis, the date of death, or the end to the follow-up period (May 2001), whichever came first. Risks for ESCC, GCC and GNCC were examined separately. Cox proportional hazard models were used to estimate relative risks (RR) with 95% confidence intervals (CI) and to adjust for potential confounders.

Ever smokers were defined as those who had ever smoked regularly for at least 6 months. Current smokers were those who had smoked regularly at the time the interview was conducted. The amount of tobacco used by pipe smokers was converted to the number of cigarette equivalents (1 g tobacco = 0.8 cigarettes). Intensity and duration analyses included both current and ex-smokers. For the dietary analysis, the consumption frequency of each food item was converted into frequency per year and categorized further into quartiles or divided into 2 groups, ever *vs.* never. The RR for cancer were calculated with the lowest consumption category as the referent. Tests for trend were carried out by assigning a single ordinal variable, 1–3 or more, to each category evaluated.

All *p*-values came from the likelihood ratio test comparing nested models and were 2-sided. The assumptions for the Cox proportional hazards model were checked and found to be valid in all cases, with the exception of BMI in relation to ESCC.

Results

During the total 15-year follow-up, 3,410 incident cancer cases (1,958 ESCC, 1,089 GCC, and 363 GNCC) were diagnosed in the cohort. The mean age of the cohort at the start of follow-up was 52 years. Table I presents the distribution of demographic and lifestyle factors for the entire cohort and for study subjects who developed each of these cancers. Consumption of tobacco and alcohol was low among people in the cohort. Compared to those in the total cohort, those who developed cancer were slightly older, more likely born in Linxian, less likely to have any formal education and more likely ever smokers.

Table II examines associations between age, gender, anthropometric variables and socioeconomic status (SES) factors and cancer risk. For ESCC, age, height and being born in Linxian were directly related and BMI, education and piped water were inversely related to risk. For GCC, age, male gender and being born in Linxian were all positively associated and education and piped water were inversely associated with risk. For GNCC, age and male gender were directly related and weight and BMI were inversely related to risk.

Relative risks associated with tobacco exposure are shown in Table III. Analyses for smoking were carried out exclusively in men, because $<1\%$ of women smoked. Cigarette and pipe smoking were both risk factors for ESCC. Ever smokers of cigarettes or pipes as well as current cigarette smokers were at higher risk for ESCC compared to non-smokers. The relative risks increased with duration of cigarette or pipe smoking. There was no significant trend in risk for cigarette or pipe smoking intensity after adjustment for duration.

Only pipe smoking was associated with GCC. As with cigarette smoking and ESCC, the relative risks rose with duration of pipe smoking, but not with pipe smoking intensity. For GNCC, an increased risk associated with smoking was seen only in current cigarette smokers and with increasing duration of cigarette smoking. There was no significant trend in risk with cigarette smoking intensity. Pipe smoking had no effect on cancer at this site.

Table IV presents RR by consumption frequency of selected dietary factors. For ESCC, inverse associations were observed with high consumption of meat, eggs and fresh fruits. Consumption of persimmon bread, foods cooked in oil, fresh vegetables, pickled vegetables, moldy vegetables, hot liquids and alcohol, all prominent dietary hypotheses in this population, were unrelated to the risk. The consumption of eggs, fresh fruits and alcohol were all associated with decreased risk of GCC, whereas consumption of moldy bread was associated with increased risk. As with ESCC, consumption of persimmon bread, foods cooked in oil, meat, fresh vegetables, pickled vegetables, moldy vegetables and hot liquids was not associated with risk of GCC. No statistically significant associations were observed between any of the studied dietary items and risk of GNCC. Adjustment for smoking (ever use of any tobacco product/never) did not alter any of the dietary associations observed. We considered that education and water piped into the home might be measures of SES, so we tested the correlation between these factors and the dietary variables. Education was positively and weakly correlated with intake of meat ($r = 0.17$), eggs ($r = 0.16$), and fresh fruits ($r = 0.18$), but further adjustment for education (none/any) did not substantially alter the risk estimates for any of the dietary variables. Water piped into the home did not correlate with any dietary factors. To further explore the effect of SES, we created indicator variables using education and piped water as follows: low (no education, no piped water; 31% of cohort), high (any education, piped water; 15% of cohort), or medium (everyone else; 54% of cohort). High SES (compared to low) was associated with a RR = 0.75 (95% CI = 0.65–0.88) for ESCC, RR = 0.61 (95% CI = 0.49–0.75) for GCC, and RR = 0.98 (95% CI = 0.69–1.40) for GNCC.

In the analysis of family history of esophageal cancer (Table V), excess risks of ESCC, GCC and GNCC were observed among individuals with a family history of "esophageal cancer" (including ESCC or GCC), and the risks were elevated with increasing number of first-degree relatives diagnosed with this cancer. Further adjustment for number of first-degree relatives did not change this result. The risk of ESCC was increased among individuals who reported esophageal cancer in a parent, brother, or sister, whereas the risk of GCC was increased among those who reported esophageal cancer in a parent or their spouse. A family history of GNCC was not associated with any of the 3 cancer sites studied (data not shown).

Table VI presents a summary of significant risk and protective factors found in our study.

Discussion

We evaluated risk factors for ESCC, GCC and GNCC in a well-defined cohort in Linxian, China, in the largest prospective study of cancers of these sites reported to date. Overall, our findings indicated that age and a family history of esophageal cancer were risk factors for all 3 cancer sites. We also identified many site-specific risk or protective factors. Cigarette smoking and pipe smoking were both risk factors for ESCC, whereas only pipe smoking was a risk factor for GCC, and only cigarette smoking

TABLE 1 – CHARACTERISTICS OF STUDY PARTICIPANTS

Characteristic	Total cohort	Esophageal cancers			Gastric cardia cancers			Gastric noncardia cancers		
		Total	Male	Female	Total	Male	Female	Total	Male	Female
n	29,584	1,958			1,089			363		
Age (years), median	52	55	55	54	55	55	55	57	58	55
(25–75%)	(44–59)	(49–61)	(49–61)	(48–60)	(49–61)	(50–61)	(49–61)	(50–62)	(51–63)	(49–60)
<50, %	42	28	26	31	25	25	27	23	21	27
50–59, %	35	42	42	42	44	44	44	39	37	44
≥60, %	23	30	32	27	31	31	30	38	42	29
Gender (male)	45	49			61			66		
Ever smoke, %										
Cigarette	30	36	73	3	42	69	47	48	72	81
Pipe	8	12	25	0	16	27	0	17	25	0
Cigarette or pipe	30	36	73	3	42	69	47	48	73	81
Cigarette pack-years: median	16	17	17	1	17	17	6	17	17	5
(25–75%)	(8–25)	(9–26)	(9–26)	(0–3)	(9–26)	(9–26)	(2–11)	(9–27)	(9–27)	(5–5)
Pipe pack-year equivalents:	3	3	3	0	3	3	0	3	3	0
median (25–75%)	(1–7)	(1–9)	(1–9)		(1–9)	(1–9)		(1–11)	(1–11)	
Pack-years (cigarette and	17	18	18	1	19	19	6	18	18	5
pipe): median (25–75%)	(8–27)	(10–29)	(10–29)	(0–3)	(9–30)	(9–30)	(2–11)	(11–31)	(12–31)	(5–5)
Alcohol (any in previous	23	23	38	8	24	34	9	24	35	3
12 months), %										
BMI (kg/m^2): median	22	21	21	21	22	21	22	21	21	22
(25–75%)	(20–23)	(20–23)	(20–23)	(20–23)	(20–23)	(20–23)	(20–24)	(20–23)	(20–22)	(20–23)
Born in Linxian	96	98	98	98	98	98	97	99	99	98
Education, %										
No formal education	40	46	23	68	44	25	75	38	23	66
1–5 years	31	32	50	14	33	47	12	40	50	19
Completed primary school	11	8	13	4	10	14	3	10	13	5
Middle school	9	5	9	2	5	9	0	5	8	0
Other/unknown	9	9	5	13	8	6	10	7	6	11
Water piped into the home, %	25	22	22	22	21	22	20	25	24	26
Family history of esophageal	27	34	32	36	31	31	32	32	29	37
cancer[1], %										
Family history of stomach	3	3	2	3	3	2	3	3	3	3
cancer[2], %										
Family history of any kind of	32	38	36	41	35	35	35	35	32	42
cancer[3], %										

[1]ESCC or GCC in one or more first-degree relatives (father, mother, siblings, or children).–[2]GNCC in one or more first-degree relatives (father, mother, siblings, or children).–[3]Any kind of cancer in one or more first-degree relatives (father, mother, siblings, or children).

TABLE II – RR AND 95% CI FOR CANCERS OF THE ESOPHAGUS, CARDIA, AND NONCARDIA ACCORDING TO SELECTED CHARACTERISTICS[1]

Characteristic	Esophageal cancers		Gastric cardia cancers		Gastric noncardia cancers	
	RR	95% CI	RR	95% CI	RR	95% CI
Age (10 years)[2]	1.64	1.55–1.72	1.73	1.61–1.85	1.98	1.75–2.24
Gender (male)[3]	1.04	0.91–1.19	1.86	1.58–2.20	2.09	1.55–2.81
Height (m)						
Q1 < 1.53	1.0	—	1.0	—	1.0	—
Q2 1.53–1.57	1.08	0.94–1.24	1.05	0.86–1.29	1.32	0.92–1.88
Q3 1.58–1.63	1.06	0.92–1.24	1.13	0.91–1.40	1.14	0.77–1.67
Q4 ≥ 1.64	1.28	1.08–1.52	1.19	0.94–1.50	1.06	0.70–1.60
Trend *p*		0.009		0.132		0.821
Weight (kg)						
Q1 <50	1.0	—	1.0	—	1.0	—
Q2 50–54	0.89	0.78–1.01	1.15	0.95–1.38	1.19	0.87–1.62
Q3 55–59	0.92	0.80–1.05	1.09	0.90–1.32	0.91	0.65–1.26
Q4 ≥ 60	0.86	0.75–0.98	1.10	0.91–1.34	0.68	0.48–0.96
Trend *p*		0.056		0.554		0.003
BMI (kg/m^2)						
Q1 < 20	1.0	—	1.0	—	1.0	—
Q2 20–21	0.96	0.85–1.08	0.98	0.84–1.16	1.00	0.76–1.32
Q3 22	0.80	0.71–0.91	0.96	0.81–1.13	0.91	0.68–1.20
Q4 ≥ 23	0.81	0.72–0.92	0.95	0.80–1.13	0.68	0.49–0.93
Trend *p*		<0.001		0.511		0.017
Born in Linxian	2.10	1.50–2.94	1.48	1.00–2.21	2.37	0.98–5.74
Education						
No formal education	1.0	—	1.0	—	1.0	—
1–5 years	0.87	0.77–0.98	0.73	0.62–0.86	1.06	0.81–1.39
Completed primary school	0.78	0.64–0.94	0.72	0.56–0.92	1.08	0.71–1.65
Middle school	0.57	0.45–0.73	0.49	0.36–0.66	0.65	0.37–1.13
Other/unknown	0.95	0.81–1.12	0.81	0.64–1.02	0.98	0.65–1.49
Water piped into the home	0.86	0.78–0.96	0.81	0.70–0.94	0.99	0.78–1.26

[1]Adjusted for age and gender.–[2]Adjusted for gender only.–[3]Adjusted for age and smoking.

was a risk factor for GNCC. Other risk factors found in our study included being born in Linxian and increased height for ESCC, male gender and consumption of moldy breads for GCC, and male gender for GNCC. In contrast, formal education, having water piped into the home and consumption of eggs and fresh fruits were all inversely associated with ESCC and GCC, whereas increased BMI was related inversely to the risk of ESCC and GNCC. In addition, consumption of meat was inversely associated with ESCC, alcohol use was inversely related to GCC and increased weight was inversely associated with GNCC.

In low-risk populations throughout the world, ESCC is more common in men, with a male:female ratio around 3–4:1.[3] In high-risk populations, however, women are affected nearly as often as men, and the gender ratio approaches or even falls below 1:1.[3,18] In our study, there was no gender preference among ESCC cases, similar to the results in other high-risk groups. Gastric cancer, on the other hand, is a male-predominant disease in all populations,[19] and in our study the male:female ratio was close to 2:1 for both GCC and GNCC.

Consumption of tobacco is a major determinant of ESCC in the United States[7,20,21] and other Western countries,[3,8,22] but this is not the case in Linxian. In this population, about half of the ESCC cases occur in women, but <1% of the women smoke. About 60% of men in Linxian smoke, but even among men, smoking is only a mild risk factor (RR = 1.33), possibly because these smokers generally consume relatively small amounts of tobacco (a median of 9–10 cigarettes/day). All 3 upper gastrointestinal cancer sites were associated with smoking in some manner, but the associations between cigarette smoking or pipe smoking and risk were site-specific. The cigarette smoking effect was restricted to ESCC and GNCC, with no association observed for GCC. For ESCC, the risk was consistently observed in ever smokers and current smokers, and increased with duration of smoking. The association with GNCC was not as clear as for ESCC, and it was limited to current smokers and duration of smoking. The effect of pipe smoking was limited to ESCC and GCC. It was strong and consistent for both of these sites, and remained significant even after adjustment for cigarette smoking (data not shown). For both cigarette and pipe smoking, adjustment for duration of smoking removed the association with intensity, but adjustment for intensity enhanced the association with duration, indicating that smoking duration was the primary determinant of risk. The simple dichotomous variable, ever smoker *vs.* never smoker, seemed to capture the overall effect of cigarette or pipe smoking for each of the 3 cancer sites studied.

In our previous 5-year prospective analysis of this cohort, we examined cigarette and pipe smoking combined as a single smoking variable and GCC and GNCC combined as stomach cancer, and we observed no significant association between stomach cancer and smoking.[9] This combined analysis did not allow evaluation of the relationships between types of smoking and cancer subsites seen in the current analysis.

Pipe smokers in Linxian use long stem pipes and unprocessed tobacco made from sun-dried leaves, whereas the tobacco in cigarettes has been processed and treated with chemicals to lower the tar and nicotine content. It is possible that this difference in processing may influence the effect of cigarette *vs.* pipe smoking on the cancer sites studied here.

Although alcohol drinking is a strong risk factor for ESCC in the West,[7,8] our study found a mild inverse association with alcohol drinking. This inverse association extended to all 3 cancer sites but was statistically significant only for GCC. The relation between alcohol drinking and risk of upper gastrointestinal cancers has been examined in several studies in China. Studies in rural, high-risk areas where alcohol drinking is rare have typically found alcohol drinking unrelated to risk[9,17] or a mild non-significant protective factor.[10,23] In contrast, studies in urban, low-risk areas have found that alcohol drinking is strongly related to risk.[24,25] The null or inverse association between alcohol drinking and upper gastrointestinal cancer in rural high-risk areas of China is likely due to the very low consumption of alcohol in these areas and the

TABLE III – RR AND CORRESPONDING 95% CI FOR CANCERS OF THE ESOPHAGUS, CARDIA, AND NONCARDIA AMONG MEN ACCORDING TO SMOKING CHARACTERISTICS[1]

Characteristic	Esophageal cancers		Gastric cardia cancers		Gastric noncardia cancers	
	RR	95% CI	RR	95% CI	RR	95% CI
Ever smoke						
Cigarette	1.34	1.16–1.54	1.10	0.93–1.30	1.30	0.98–1.72
Pipe	1.31	1.13–1.53	1.48	1.24–1.77	1.21	0.90–1.63
Cigarette or pipe	1.33	1.15–1.53	1.10	0.94–1.30	1.30	0.98–1.72
Current cigarette smoker	1.32	1.15–1.51	1.12	0.96–1.32	1.40	1.07–1.85
Current pipe smoker	1.33	0.94–1.88	1.39	0.93–2.10	1.17	0.60–2.38
Cigarette intensity (cigarettes/day) (also adjusted for cigarette duration)						
0	1.0	—	1.0	—	1.0	—
Q1 < 7	1.06	0.79–1.42	1.01	0.71–1.43	1.08	0.60–1.95
Q2 7–9	1.61	1.06–2.44	0.62	0.32–1.21	1.06	0.42–2.67
Q3 10–19	1.27	0.95–1.70	1.02	0.72–1.45	1.17	0.65–2.12
Q4 ≥ 20	1.12	0.83–1.51	1.00	0.70–1.44	0.91	0.49–1.70
Trend *p*		0.412		0.873		0.638
Cigarette duration (years) (also adjusted for cigarette intensity)						
0	1.0	—	1.0	—	1.0	—
Q1 < 19	1.31	1.03–1.68	1.01	0.74–1.38	1.07	0.61–1.86
Q2 19–27	1.25	0.97–1.61	1.14	0.84–1.55	1.47	0.88–2.46
Q3 28–35	1.34	1.07–1.69	1.26	0.96–1.66	1.60	1.01–2.51
Q4 ≥ 36	1.60	1.26–2.03	1.16	0.87–1.54	1.77	1.12–2.77
Trend *p*		<0.001		0.155		0.007
Pipe intensity (cigarette equivalents/day) (also adjusted for pipe duration)						
0	1.0	—	1.0	—	1.0	—
Q1 < 3	1.10	0.83–1.44	1.04	0.74–1.45	0.93	0.53–1.61
Q2 3–4	1.28	0.90–1.82	1.89	1.30–2.74	1.24	0.63–2.46
Q3 5–6	0.95	0.70–1.29	1.15	0.81–1.64	1.04	0.58–1.85
Q4 ≥ 7	0.89	0.62–1.28	1.25	0.84–1.86	0.70	0.33–1.49
Trend *p*		0.573		0.144		0.649
Pipe duration (years) (also adjusted for pipe intensity)						
0	1.0	—	1.0	—	1.0	—
Q1 < 4	1.28	0.94–1.76	1.24	0.84–1.82	1.44	0.81–2.58
Q2 4–10	1.11	0.79–1.55	1.26	0.86–1.85	0.91	0.46–1.77
Q3 11–27	1.28	0.92–1.78	1.79	1.26–2.55	0.92	0.46–1.85
Q4 ≥ 28	1.97	1.44–2.68	1.75	1.20–2.54	1.71	0.94–3.11
Trend *p*		<0.001		0.001		0.275
Total smoking duration (cigarette and pipe combined) (years) (also adjusted for cigarette and pipe intensity)						
0	1.0	—	1.0	—	1.0	—
Q1 < 20	1.19	0.92–1.53	0.88	0.64–1.21	1.09	0.63–1.89
Q2 20–28	1.29	1.01–1.66	1.13	0.83–1.53	1.40	0.84–2.35
Q3 29–36	1.31	1.04–1.65	1.31	1.00–1.71	1.56	0.99–2.45
Q4 ≥ 37	1.52	1.19–1.94	1.22	0.90–1.64	1.85	1.16–2.94
Trend *p*		0.001		0.048		0.007

[1]Adjusted for age.

fact that alcohol drinking is probably correlated with SES in these populations.

High consumption of vegetables and fruits is associated with a reduced risk of cancer in many studies around the world.[26] Vegetables and fruits are rich in antioxidant micronutrients (*e.g.*, carotenoids, ascorbate, vitamin E, selenium) and other bioactive compounds with a variety of potent anticarcinogenic properties (*e.g.*, phenols, flavonoids, isoflavones).[27] Results of 3 previous studies in Linxian regarding consumption of fresh vegetables have been mixed: one found a significant inverse association with ESCC/GCC,[10] another found a non-significant inverse association with ESCC[9] and a third reported that high consumption of fresh vegetables was associated with a significant 40–50% increased risk of ESCC/GCC.[17] None of these studies found an association between consumption of fresh fruits and ESCC or GCC.[9,10,17] Our present study found no association with fresh vegetable intake, but did observe a protective association between consumption of fresh fruits and risk of ESCC and GCC.

Increased consumption of meat and eggs was also associated with reduced risk of ESCC. In addition to the nutritional value of these specific food items, higher meat and egg consumption may also reflect better overall nutrition and higher SES. There was no relation between consumption of persimmon breads, moldy vegetables or pickled vegetables and risk of cancer at any of the 3 sites studied. Consumption of these items was very low, however, probably due to the mass public health campaigns in the 1970s that urged residents to avoid these items.[9]

The absence of associations between selected dietary variables and upper gastrointestinal cancers in our study may be due to a true lack of effect or due to limitations in our study, such as inaccurate questionnaire responses (*e.g.*, misclassification as is typical in food frequency questionnaires; or systematic under-reporting, particularly for proscribed items such as pickled or moldy foods) or insufficient variation in intake of a food item in the cohort. Comparing the ratio of the 75th to the 25th percentiles of intake, the foods with the highest variability in intake, including meat (3-fold), eggs (18-fold) and fresh fruits (13-fold), showed significant protective associations, whereas foods with less variability in intake, such as fresh vegetables (1.7-fold), did not.

The inverse association between increasing BMI and risk of ESCC and GCC further supports the hypothesis that poor overall nutrition is a risk factor for these cancers. The highest quartile of BMI in Linxian was only ≥23, which is well within the normal BMI range (18.5–24.9) in the United States.[28] Surprisingly, height, which is determined by the adequacy of nutrition during adolescence, was associated with increased risk of ESCC.

In addition to lifestyle factors, genetic factors also influence the occurrence of upper gastrointestinal cancers in Linxian. Indeed, a family history of esophageal cancer (including ESCC or GCC) is

TABLE IV – RR AND 95% CI FOR CANCERS OF THE ESOPHAGUS, CARDIA, AND NONCARDIA ACCORDING TO CONSUMPTION OF SELECTED FOOD[1]

Times/year	Total cohart, %	Esophageal cancers		Gastric cardia cancers		Gastric noncardia cancers	
		RR	95% CI	RR	95% CI	RR	95% CI
Persimmon bread							
0	95	1.0	—			1.0	—
≥ 1	5	1.10	0.89–1.35	1.11	0.85–1.46	0.79	0.45–1.38
Foods cooked in oil							
≤ 6	29	1.0	—	1.0	—	1.0	—
> 6–12	40	1.06	0.95–1.18	0.83	0.71–0.96	1.12	0.86–1.45
> 12–24	16	1.01	0.88–1.16	0.98	0.82–1.17	1.35	0.99–1.84
> 24	15	1.04	0.90–1.20	0.86	0.71–1.04	0.92	0.65–1.31
Trend *p*			0.716		0.319		0.830
Meat							
≤ 4	26	1.0	—	1.0	—	1.0	—
> 4–9	24	0.92	0.81–1.04	0.94	0.79–1.11	1.03	0.76–1.39
> 9–12	36	0.94	0.84–1.05	0.92	0.79–1.08	1.14	0.87–1.50
> 12	14	0.73	0.62–0.86	0.89	0.72–1.09	0.87	0.60–1.26
Trend *p*			0.003		0.213		0.961
Eggs							
≤ 2	28	1.0	—	1.0	—	1.0	—
> 2–10	24	0.99	0.87–1.11	0.83	0.70–0.98	0.85	0.63–1.15
> 10–36	27	0.92	0.82–1.04	0.91	0.77–1.06	1.15	0.87–1.51
> 36	21	0.85	0.75–0.97	0.76	0.64–0.90	0.99	0.73–1.33
Trend *p*			0.011		0.008		0.562
Fresh vegetables							
≤ 549	32	1.0	—	1.0	—	1.0	—
> 549–732	29	0.93	0.83–1.05	0.94	0.80–1.10	1.30	0.99–1.71
> 732–915	28	1.01	0.90–1.13	1.03	0.88–1.20	1.43	1.09–1.87
> 915	11	1.02	0.88–1.19	1.17	0.96–1.42	1.04	0.71–1.53
Trend *p*			0.696		0.153		0.156
Pickled vegetables							
0	100	1.0	—	1.0	—	1.0	—
≥ 1	0	0.95	0.81–1.12	1.04	0.85–1.29	1.09	0.76–1.56
Moldy vegetables							
0	100	1.0	—	1.0	—	1.0	—
≥ 1	0	1.02	0.51–2.04	1.41	0.63–3.13	0.71	0.10–5.04
Fresh fruits							
≤ 1	27	1.0	—	1.0	—	1.0	—
> 1–5	23	0.84	0.74–0.95	1.02	0.86–1.20	0.99	0.73–1.33
> 5–13	25	0.89	0.79–1.00	0.84	0.71–1.00	1.14	0.86–1.51
> 13	24	0.80	0.70–0.91	0.89	0.75–1.05	0.95	0.71–1.28
Trend *p*			0.002		0.047		0.965
Moldy bread							
0	82	1.0	—	1.0	—	1.0	—
≥ 1	18	0.97	0.86–1.09	1.18	1.01–1.37	0.93	0.71–1.23
Hot liquid in summer							
0	25	1.0	—	1.0	—	1.0	—
≥ 1	75	0.96	0.87–1.07	1.05	0.90–1.21	1.12	0.86–1.45
Hot liquid in winter							
0	52	1.0	—	1.0	—	1.0	—
≥ 1	48	0.95	0.87–1.04	0.98	0.87–1.11	1.09	0.88–1.35
Alcohol (any in previous 12 mos)	23	0.92	0.82–1.03	0.84	0.72–0.97	0.79	0.61–1.02

[1]Adjusted for age and gender.

one of the most consistent risk factors for these cancers in this population.[9,10,17] In our study, increased risk of the ESCC and GCC were found among people with a family history of esophageal cancer, and the risk increased with the number of first-degree relatives who had this disease. The role of genetics in the development of esophageal cancer is also supported by previous reports of familial aggregation of esophageal cancer[29,30] and by one segregation analysis of esophageal cancer pedigrees that suggested an autosomal recessive Mendelian inheritance pattern.[31] Recent molecular studies also support a role for genetic susceptibility in the etiology of ESCC in this area. Preliminary studies have shown high frequencies of loss of heterozygosity (LOH),[32] characteristic patterns of gene expression[33] and significant differences in both LOH and gene expression by family history[33,34] in ESCC tumors from a high-risk population in neighboring Shanxi Province. In addition, genetic polymorphisms in folate-metabolizing genes have been shown to predispose individuals to esophageal and gastric cancer in Linxian.[35]

Our study has several strengths, including its prospective design, large sample size, 15-year follow-up, and large number of verified cancer cases, which allowed us to observe precise and unbiased estimates of even moderate associations that could easily be missed in smaller studies. We determined the risk for cancer incidence rather than cancer death, which avoided potential bias related to medical treatment or the effects of disease. Our study also included the largest number of ESCC and GCC cases studied to date, which allowed us to investigate and compare risks by anatomic subsites with statistical precision. Our analysis was limited, however, by insufficient variation in the distribution of many possible risk and protective factors, especially dietary variables. Furthermore, it is possible that associations with risk cannot be attributable to specific food items per se, but rather to poor overall diet as evidenced by the few times participants consumed meat, fresh fruits or eggs each year. The lack of *Helicobacter pylori* infection data for the entire cohort in our present study may represent a limitation because a previous nested case-control study

TABLE V – RR AND 95% CI FOR CANCERS OF THE ESOPHAGUS, CARDIA, AND NONCARDIA IN RELATION TO FAMILY HISTORY OF ESOPHAGEAL CANCER[1]

Characteristic	Total cohort, %	Esophageal cancers		Gastric cardia cancers		Gastric noncardia cancers	
		RR	95% CI	RR	95% CI	RR	95% CI
Family history of esophageal cancer[2,3]							
No	73	1.0	—	1.0	—	1.0	—
Yes	27	1.42	1.29–1.56	1.25	1.10–1.43	1.27	1.02–1.59
Types of relatives with esophageal cancer							
Father	13	1.26	1.11–1.42	1.24	1.05–1.46	1.32	1.00–1.75
Mother	13	1.56	1.39–1.75	1.18	1.00–1.46	1.14	0.85–1.53
Brother	4	1.31	1.07–1.60	1.26	0.96–1.67	1.02	0.61–1.72
Sister	2	1.50	1.18–1.92	1.27	0.90–1.67	1.55	0.91–2.65
Son	< 1	2.21	0.55–8.84	3.44	0.86–13.80	—	—
Daughter	< 1	—	—	—	—	—	—
Spouse	3	1.06	0.83–1.36	1.35	1.01–1.81	0.85	0.46–1.55
Number of first-degree relatives with esophageal cancer[2]							
0	73	1.0	—	1.0	—	1.0	—
1	23	1.32	1.20–1.47	1.22	1.06–1.40	1.24	0.98–1.57
> 1	4	1.89	1.59–2.25	1.44	1.12–1.86	1.45	0.94–2.24
Trend *p*			<0.001		<0.001		0.028

[1]Adjusted for age and gender.–[2]Adjusted for age, gender, and number of first degree relatives.–[3]ESCC or GCC in one or more first-degree relatives (father, mother, siblings, or children).

TABLE VI – SUMMARY OF SIGNIFICANT RISK (↑) AND PROTECTIVE (↓) FACTORS FOUND IN THIS STUDY

Factor	ESCC	GCC	GNCC
Risk factors			
Age	↑	↑	↑
Gender (male)		↑	↑
Cigarette smoking	↑		↑
Pipe smoking	↑	↑	
Height	↑		
Born in Linxian	↑		
Family history of esophageal cancer	↑	↑	↑
Moldy bread		↑	
Protective factors			
Alcohol		↓	
Weight			↓
BMI	↓		↓
Education (any)	↓	↓	
Water piped into the home	↓	↓	
Meat	↓		
Eggs	↓	↓	
Fresh fruits	↓	↓	

of this same population found an increased risk of both GCC and GNCC among individuals with *Helicobacter pylori* infection.[36] Using data for 192 controls from the previous study, however, no significant correlations between *Helicobacter pylori* infection and age, gender, height, weight, BMI, birthplace, education and water supply were found (data not shown). Thus, confounding by *Helicobacter pylori* infection is unlikely to account for the results in our study.

A common theme and potential explanation for many of the disease associations seen in our study is low SES. The poor nutritional status of the Linxian population in 1984, reflected by the dietary data and the low BMI recorded in our study, is a serious matter, and efforts to improve the diet, particularly the availability of a greater variety of affordable foods, continue to be a public health priority in Linxian. Our results suggest that such efforts to improve the SES of the Linxian population are likely to have substantial beneficial effects on the health of the people living there, and such effects may already be evident in the recent reports suggesting a decline in the rates of ESCC/GCC in this area.[6]

In conclusion, we carried out a large prospective cohort study in Linxian, China and identified a variety of risk and protective factors for 3 upper gastrointestinal cancers (ESCC, GCC and GNCC). Age and a family history of esophageal cancer were risk factors for all 3 cancers, and male gender was a risk factor for GCC and GNCC. Additional risk factors included being born in Linxian, increased height, cigarette smoking and pipe smoking for ESCC, consumption of moldy bread and pipe smoking for GCC and cigarette smoking for GNCC. In our study, formal education, having water piped into the home and eating more eggs and fresh fruits were protective factors for ESCC and GCC. Additional protective factors included increased consumption of meat and increased BMI for ESCC, alcohol consumption for GCC, and increased weight and BMI for GNCC. Our results suggest that tobacco smoking is a risk factor in Linxian, but that its influence is modest, and that other lifestyle factors associated with low SES are more important. General SES improvement may have an effect on many of these factors and is a promising approach for reducing the burden of ESCC and GCC in Linxian.

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